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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No. : 10/715,112 Confirmation No. : 5872  
Applicant : Claudia BERGER, et al.  
Filed : November 18, 2003  
TC/A.U. : 1614  
Examiner : Unassigned  
Docket No. : 029300.52857US  
Customer No. : 23911  
Title : Compounds with NEP/MP- Inhibitory Activity and Uses  
Thereof

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT  
UNDER 37 C.F.R § § 1.97 AND 1.98**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

This supplements the Information Disclosure Statement submitted in the  
above-identified application on May 5, 2004.

In accordance with the duty of disclosure under 37 C.F.R. § 1.56, Applicant  
hereby notifies the U.S. Patent and Trademark Office of the documents which  
are listed on the attached Form PTO-1449 and/or listed herein and which the  
Examiner may deem relevant to patentability of the claims of the above-  
identified application.

**STATEMENT OF RELEVANCE**

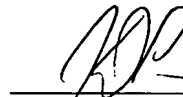
The relevance of these references to the subject matter of the present  
invention is given in the specification of the present invention.

English abstracts are submitted herewith for the references listed on the  
PTO 1449 as AQ, AS-AU.

The present Information Disclosure Statement is being filed (1) no later than three months from the application's filing date or (2) before the mailing date of the first Office Action on the merits (whichever is later), and therefore no certification under 37 C.F.R. § 1.97(e) or fee under 37 C.F.R. § 1.17(p) is required.

The submission of the listed documents is not intended as an admission that any such document constitutes prior art against the claims of the present application. Applicant does not waive any right to take any action that would be appropriate to antedate or otherwise remove any listed document as a competent reference against the claims of the present application.

Respectfully submitted,

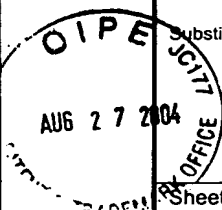


J. D. Evans  
Registration No. 26,269

August 27, 2004

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Substitute for form 1449A/PTO

**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**

(use as many sheets as necessary)

Sheet 1 of 7

**Complete if Known**

Application Number	10/715,112
Filing Date	November 18, 2003
First Named Inventor	Claudia BERGER
Art Unit	1614
Examiner Name	Unassigned
Attorney Docket Number	029300.52857US

**U.S. PATENT DOCUMENTS**

Examiner Initials <sup>1</sup>	Cite No. <sup>1</sup>	Document Number Number-Kind Code <sup>2</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA	US- 6,548,284	04-15-2003	Masafumi Matsuo et al.	
	AB	US- 6,482,820	11-19-2002	Martin R. Wilkins et al.	
	AC	US- 5,965,425	10-12-1999	Phillip J. Barr et al.	
	AD	US- 2003/0119714	06-26-2003	Alasdair Mark Naylor et al.	
	AE	US- 2002/086405	07-04-2002	Inmaculada Silos-Santiago et al.	
	AF	US- 2002/0177689	11-28-2002	Neil Benson et al.	
	AG	US- 2002/0102707	08-01-2002	Ian Dennis Harrow et al.	

**FOREIGN PATENT DOCUMENTS**

Examiner Initials <sup>1</sup>	Cite No. <sup>1</sup>	Foreign Patent Document Country Code <sup>3</sup> -Number <sup>4</sup> -Kind Code <sup>5</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T <sup>6</sup>
	AH	WO 03/51 370	06-26-2003	Pfizer Limited		
	AI	WO 03/40 393	05-15-2003	Decode Genetics EHF		
	AJ	WO 02/06 492	01-24-2002	Pfizer Limited		
	AK	WO 02/26 958	04-04-2002	Millennium Pharmaceuticals, Inc.		
	AL	WO 02/47 670	06-20-2002	Pfizer Limited		
	AM	WO 02/08396	01-31-2002	Incyte Genomics, Inc.		
	AN	WO 02/094176	11-28-1992	Solvay Pharmaceuticals GmbH		
	AO	WO 01/83782	11-08-2001	Sugen Inc.		

Examiner  
SignatureDate  
Considered

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

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Sheet	2	of	7	Attorney Docket Number	029300.52857US

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		Country Code <sup>3</sup> —Number <sup>4</sup> —Kind Code <sup>5</sup> (if known)				
	AP	WO 01/36610	05-25-2001	Solvay Pharmaceuticals B.V.		
	AQ	WO 01/03699	01-18-2001	Solvay Pharmaceuticals GmbH		AB
	AR	WO 00/47750	08-17-2000	Universtie De Montreal		
	AS	WO 00/48 601	08-24-2000	Solvay Pharmaceuticals GmbH		AB
	AT	WO 99/53 077	10-21-1999	Institut National De La Sante Et De La Recherche Medicale		AB
	AU	EP 1069 188	01-17-2001	Sanofi-Synthelabo		AB
	AV	EP 1 275 733	01-15-2003	Pfizer Limited		
	AW	EP 1 308 459	05-07-2003	Helix Research Institute		

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>2</sup>
	AX	AM BOLLEN ET AL., "Purification and Characterization of a Soluble Endopeptidase from Rat Bone", Calcified Tissue International, 1991, pp. 111-119, Springer-Verlag New York, Inc.	

Examiner Signature		Date Considered	
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			Filing Date	November 18, 2003	
			First Named Inventor	Claudia BERGER	
			Art Unit	1614	
Examiner Name	Unassigned				
Sheet	3	of	7	Attorney Docket Number	029300.52857US

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>2</sup>
	AY	T.A. VIDA ET AL. "Glycosylation Variants of Endopeptidase-24.11 ('Enkephalinase')", Neuroptides, 1992, pp.245-255, Vol. 21, ISSN: 0143-4179	
	AZ	K. SHIROTANI ET AL. " Neprilysin Degrades Both Amyloid $\beta$ Peptides 1-40 and 1-42 Most Rapidly and Efficiently among Thiorphan- and Phosphoramidon-sensitive Endopeptidases", The Journal of Biological Chemistry, June 15, 2001, Vol 276, No. 24, pp. 21895-21901, The American Society for Biochemistry and Molecular Biology, Inc., United States	
	BA	P. FACCHINETTI ET AL., " Ontogeny, Regional and Cellular Distribution of the Novel Metalloprotease Neprilysin 2 In the Rat: A Comparison with Neprilysin and Endothelin-Converting Enzyme-1", Neuroscience 118, 2003, pp. 627-639, Elsevier Science Ltd.	
	BB	MARC J. GLUCKSMAN ET AL., "Strategies for Characterizing, Cloning, and Expressing Soluble Endopeptides", Methods in Neuroscience, 1995, pp. 296-316, Volume 23, Academic Press Inc.	
	BC	WILLIAM G. HAYNES ET AL., " Endothelin as a Regulator of Cardiovascular Function in Heath and Disease", Journal of Hypertension, 1988, Vol. 16, pp. 1081-1098, Lippincott-Raven Publishers	
	BD	KOJI IKEDA ET AL., "Molecular Identification and Characterization of Novel Membrane-bound Metalloprotease, the Soluable Secreted Form of Which Hydrolyzes a Variety of Vasoactive Peptides", J. Biol. Chem, November 5, 1999, pp. 32469-32477, Vol. 274, Issue 45	
	BE	ANN BEAUMONT ET AL., " Evidence That Both Arginine 102 and Arginine 747 Are Involved in Substrate Binding to Neutral Endopeptidase (EC 3.4.24.11)", The Journal of Biological Chemistry", January 5, 1991, pp. 214-220, Vol. 266, No. 1, The American Society for Biochemistry and Molecular Biology, Inc.	

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	BF	ERIMINIO COSTA ET AL., "Opioid Peptide Biosynthesis: Enzymatic Selectivity and Regulatory Mechanisms, 1987, pp. 16-21, FASEB	
	BG	PHILIPPE CRINE ET AL., "The Production and Characterization of a Monoclonal Antibody Specific for the 94,000 Dalton Enkephalin-Degrading Peptidase from Rabbit Kidney Brush Border," Biochemical and Biophysical Research Communications, August 30, 1985, pp. 255-261, Vol. 131, No. 1, Academic Press Inc.	
	BH	NATALIE DION ET AL., "Kinetic Evidence That His-711 of Neutral Endopeptidase 24.11 is Involved in Stabilization of the Transition State", FEBS Lett., March 1993, pp. 301-304, Vol. 318, No. 3, Elsevier Science Publishers B.V.	
	BI	EC 3.4.24.15, "Nomenclature Committee of the International Union of Biochemistry", Webpage	
	BJ	ROY G. GOLDIE ET AL., "Endothelins and Asthma", Life Sciences, 1999, pp. 1-15, Vol. 65, Elsevier Science Inc., USA	
	BK	NIGEL M. HOOPER, "Families of Zinc Metalloproteases," FEBS Letters 354, 1994, pp 1-6, 1994 Federation of European Biochemical Societies	
	BL	HERVÉ LE MOUAL ET AL., "Identification of Glutamic Acid 646 as a Zinc-Coordinating Residue in Endopeptidase-24.11", The Journal of Biological Chemistry, August 25, 1991, pp. 15670-15674, Vol. 266, No. 24, The American Society for Biochemistry and Molecular Biology, Inc., USA	
	BM	CYNTHIA MARIE-CLAIRE ET AL., "Evidence By Site-Directed Mutagenesis That Arginine 203 of Thermolysin and Arginine 717 of Neprilysin (Neutral Endopeptidase) Play Equivalent Critical Roles in Substrate Hydrolysis and Inhibitor Binding," Biochemistry, 1997, pp. 13938-13945, 36, 1997 American Chemical Society	

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Sheet	5	of	7	Attorney Docket Number	029300.52857US

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>2</sup>
	BN	MARIAN ORLOWSKI ET AL., "A Soluable Metalloendopeptidase from Rat Brain. Purification of the Enzyme and Determination of Specificity with Synthetic and Natural Peptides," Eur J. Biochem. 1993, pp. 81-88,135, FEBS 1983	
	BO	SUNU BUDHI RAHARJO ET AL., "Alternative Splicing Regulates the Endoplasmic Reticulum Localization or Secretion of Soluble Secreted Endopeptidase," J. Biol. Chem., July 6, 2001, pp. 1-17, Vol. 276(27)	
	BP	OUIMET TANJA ET AL., "Neprilysin II: A Putative Novel Metalloprotease and Its Isoforms in CNS and Testis," Biochemical and Biophysical Research Communications, 2000, pp. 565-570, 271, Academic Press	
	BQ	CHRISTIANE ROSE ET AL, "Cell-Specific Activity of Neprilysin 2 Isoforms and Enzymic Specificity Compared with Neprilysin," Biochem. J., 2002, pp. 697-705, 363, Biochemical Society, Great Britain	
	BR	I. SOHAR ET AL., " Soluble Metalloendopeptidase (MMP-7ASE) Activity in Mouse Kidney Cytosol", Acta Biologica Hungarica, 1991, pp. 265-274, 42 (1-3), Budapest	
	BS	GALIA GHADDAR ET AL., " Molecular Cloning and Biochemical Characterization of a New Mouse Testis Soluble-Zinc-Metallopeptidase of the Neprilysin Family", Biochem J., 2000, pp. 419-429, 347, Biochemical Society, Great Britain	
	BT	PHILIPPE CRINE ET AL., "ENDOPEPTIDASE-24-11", Cell-Surface Peptidases in Health and Disease, 1997, pp. 79-98, 1997 BIOS Scientific Publishers, Oxford	
	BU	ALAIN DEVAULT ET AL., " Exploration of the Catalytic Site of Endopeptidase 24.11 by Site-Directed Mutagenesis", FEB 05746, April 1998, pp. 54-58, Vol. 231(1), Elsevier Science Publishers B.V.	

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	BV	NATALIE DION ET AL., "Evidence That Asn <sup>542</sup> of Neprilysin (EC 3.4.24.11) is Involved in Binding of the P <sub>2</sub> Residue of Substrates and Inhibitors", Biochem J., 1995, pp. 623-627, 311, Great Britain	
	BW	ROBERT J. BENYON ET AL., "Characterization of the Soluble, Secreted Form of Urinary Meprin", Biochem. J., 1996, pp. 461-466, 315, Great Britain	
	BX	NADIA BONVOULOIR ET AL., "Molecular Cloning, Tissue Distribution, and Chromosomal Localization of MMEL2, a Gene Coding for Novel Human Member of the Neutral Endopeptidase-24.11 Family", DNA and Cell Biology, November 8, 2001, pp. 493-498, Vol. 20, Mary Ann Liebert, Inc.	
	BY	STEWART BARKER ET AL., "Effect of an Antisense Oligodeoxynucleotide to Endothelin-Converting Enzyme-1c (ECE-1c) on ECE-1c mRNA, ECE-1 Protein and Endothelin-1 Synthesis in Bovine Pulmonary Artery Smooth Muscle Cells", Molecular Pharmacology, 2001, pp. 163-169, Vol. 59, No. 2, The American Society for Pharmacology and Experimental Therapeutics, USA	
	BZ	MARIAN ORLOWSKI ET AL., "Purification and Specificity of a Membrane-Bound Metalloendopeptidase from Bovine Pituitaries", Biochemistry, 1981, pp. 4942-4950, 20, American Chemical Society	
	CA	HERVÉ LE MOUAL ET AL., "Asp650 is Crucial for Catalytic Activity of Neutral Endopeptidase 24-11", Eur. J. Biochem., 1994, pp. 475-480, 221, FEBS	

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	CB	STEPHEN A. DOUGLASS, "Clinical Development of Endothelin Receptor Antagonists", TIPS, November 1997, pp. 408-412, Vol. 18, Elsevier Science Ltd.	
	CC	BERNARD P. ROQUES, "Zinc Metallopeptidases: Active Site Structure and Design of Selective and Mixed Inhibitors: New Approaches in the Search for Analgesics and Anti-Hypertensives", Biochemical Society Transactions, Vol. 21	
	CD	Derwent Drug File, "Design and Synthesis of Novel Small Molecule N/OFQ Receptor Antagonists/Effects of Nociceptin on the Exploratory Behavior of Mice in the Hole-Board Test.", GenBank, pp.1-3	

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<sup>1</sup>Applicant's unique citation designation number (optional). <sup>2</sup>Applicant is to place a check mark here if English language Translation is attached.

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